## REMARKS

In the office action, the Examiner has stated that the "specification provides sufficient support for the *in vitro* use of such a method on cells in culture, and for the *in vivo* use of spermidine in inhibiting apoptosis in rat corpus luteum." Claim 1 has been amended to include the term "in vivo" and new claim 88 has been added to claim the *in vivo* use of spermidine in inhibiting apoptosis in rat corpus luteum. Claims 2-10 and 12-86 have been caneled. Claim 87 has been amended to list the particular polyamines, as well as indicate that the levels of the polyamines administered are not to be at toxic levels. New claim 89 has been added. Accordingly, claims 1, 11 and 87-89 are pending in this application.

### Rejection under 102(b) over Tome et al.

The Examiner has maintained the anticipation rejection in light of Tome et al. (Biochem J., 328:847-854 (1997). The Examiner states that "there is no evidence that these are actually different isoforms, because it is well known in the art that a polypeptide may have more than one function." Further, the Examiner states that since they are both named eIF-5A and because both are sensitive to polyamine administration, there is strong evidence to presume that the isoforms are identical. The Examiner also states that the "applicants have not provided any arguments or evidence that the isoforms differ in structure."

In response to this rejection, the applicants submit herewith a print out of a Genbank listing that shows the entry of several isoforms of eIF-5A. This submission shows that indeed that eIF-5A exists as a couple of isoforms, and that contrary to the Examiner's notion, these isoforms are different but yet are all named eIF-5A.

In addition, applicants submit herewith a sequence alignment of two isoforms of eIF-5A. This figure shows that although there is a great deal of similarity in the sequences of the two

isoforms, there are indeed differences. The isoform listed as eIF-5A1 in the figure is what the applicant has termed the apoptosis isoform and what is the subject of the present invention. The isoform listed as eIF-5A2 is known as the isoform of eIF-5A involved in cell division or proliferation, i.e. the isoform discussed in Tome et al.

It is clear from various passages in Tome et al. that the isoform of eIF-5A in Tome is not the apoptosis isoform of the present invention. For example, in the Abstract of the Tome reference it states: "Further, these data suggest that suppression of modified eIF-5A formation is one mechanism by which cells may be induced to undergo apoptosis." (emphasis added) Also on page 853 of the Tome reference, it states:

> Support for the hypothesis that inhibition of modified eIF-5A formation may be sufficient to induce apoptosis comes from the results for DAH-treated cells. Treatment of DH23A/b cells with DAH, an *in vitro* competitive inhibitor of eIF-5A hypusinyulation, in the presence of DFMO to suppress putrescine levels causes suppression of the formation of modified eIF-5A, with a concomitant **increase** in apoptosis. (emphasis added).

Thus, using the isoform of eIF-5A discussed in Tome, if one suppresses activation of eIF-5A, the cells are induced to undergo apoptosis. Whereas, with Senesco's isoform, if one suppresses the formation of modified (activated) eIF-5A, the cells do not undergo apoptosis, as seen in Example 6. In Example 6, the cells are inhibited from apoptosis. Thus, applicants submit that since suppression of modification of Tome's isoform (increase in apoptosis) leads to the complete opposite result of the suppression of Senesco's isoform (decrease in apoptosis), it is clear that the Tome isoform is different than Senesco's isoform. As such, Tome does not anticipate nor render obvious Senesco's isoform.

Further, Tome does not teach the addition of any agent to inhibit the activation of eIF-5A to inhibit apoptosis. Rather, Tome seems to be teaching the complete opposite, the inactivation of eIF-5A to induce or increase apoptosis. Tome, therefore, does not teach the elements of the present claims and thus does not anticipate the claims under 102(b) nor renders them obvious under 103.

**Rejection under 35 U.S.C. 112, first paragraph (enablement)**

The Examiner has rejected claims 1, 3, 11, 30, 46, 47 and 87 under 35 U.S.C. 112, first paragraph. The Examiner has acknowledged that the specification provides support for the *in vitro* use of such a method on cells in culture, as well as for the *in vivo* use of spermidine in inhibiting apoptosis in rat corpus luteum. Thus, the Examiner acknowledges that the presently amended claim 1 and new claim 88 are enabled. The applicants, however, respectfully submit that the specification provides enablement for the other pending claims.

As for the other pending claims, the Examiner asserts that they are not enabled given the unpredictability of polyamines. The Applicants respectfully disagree. The unpredictability that the Examiner is referring to is the fact that polyamines can sometimes cause cell death because of their toxicity or as in the present invention, have been shown to inhibit apoptosis. However, in the Examiner's analysis, he has failed to consider the teachings of the present invention and seems to rely solely on the alleged unpredictable state of art prior to the present invention. Applicants respectfully assert that the teachings of the present invention provide ample guidance to one skilled in the art to make and use the claimed invention without undue experimentation.

The Examiner's analysis of unpredictability is erroneously focused on the prior art's understanding of only one element present in the claimed invention (polyamines) and fails to consider and appreciate that the teachings of the application dispose of this unpredictability as it relates to the claimed invention (use of polyamines to inhibit apoptosis).

As acknowledged in a previous response (and in various references cited by the Examiner), it is known that polyamines given at a high dose can be toxic to cells and thus cause cell death. The applicants do not dispute this fact and in fact the present application provides a Table on page 44 of the specification that clearly provides the LD50 levels for many of the polyamines. Nevertheless, the specification lays out in Example 6 (particularly on page 110) the doses of spermidine provided to a rat, subcutaneously, to inhibit apoptosis. The specification thus teaches the administration of a polyamine to inhibit apoptosis. The specification clearly provides teaching and enablement for administering to an animal a known amount of a polyamine to achieve the desired result - apoptosis. It is irrelevant, or the very least, not decisive to an enablement inquiry, that prior to the present invention it was not known how or if polyamines effect apoptosis, nor is it relevant that prior to the present invention it was not known that a polyamine could be administered *in vivo* to inhibit apoptosis. Just because, prior to the present invention, it was not known or appreciated that polyamines could be used to inhibit apoptosis by effecting the DHS/eIF-5A cascade, just because the effects of polyamines on cells was perceived to be unpredictable, does not in itself negate the fact that the present invention provides teaching and enablement to those skilled in the art to in fact use polyamines to inhibit apoptosis (the claimed invention). It appears that the Examiner has focused on prior confusion and unpredictability of polyamines as understood generally and before the present invention, but has failed to consider that the present invention has provided guidance and teaching and how to use the claimed invention. Just because prior knowledge of one element of a claimed invention was unpredictable or perhaps not understood, does not negate the fact that the specification provides enablement for an invention that uses that element, especially as enablement is to be determined based on the entire teaching of the application and not just the unpredictability of one element prior to the invention. It appears that the Examiner has limited his enablement inquiry to one element and not considered the teachings of how that element is used in the claimed invention.

Further, MPEP 2164.03 states that unpredictability or lack thereof in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results of the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. The claims require that the polyamine is administered at levels not to be toxic and the specification provides guidance as to the toxic levels. In addition, the specification provides the dosage of spermidine given to a rat and also provides dosage amounts per body weight needed to inhibit apoptosis. Thus, one skilled in the art would be able to use the provided rat data and apply it to other animal models and other cell types without undue experimentation. He would be guided by the dosage levels provided in the specification to administer, as well as guided by the toxic levels disclosed as the absolute upper boundary not to administer. One skilled in the art is familiar with extrapolating data from one animal model and applying it to another animal model without necessarily undergoing undue experimentation, especially in light of the present application's teaching of dosages per animal body weight. Further, the specification also demonstrates that there is a correlation between *in vitro* and *in vivo* data. For example, Example 5 provides data where apoptosis is inhibited in rat corpus luteum cells *in vitro* by treatment with a polyamine. Then, in Example 6, it is shown that the same polyamine inhibits apoptosis when administered to a rat *in vivo*. Thus, not only does the present invention provide a working example with data that can be extrapolated for other animals and cells, it also provides one skilled in the art a model for *in vitro* testing that correlates with *in vivo* results. Thus, the specification provides tools and enablement to practice the invention without undue experimentation.

As to methods of administration, the working example in the specification employs subcutaneous administration, but it also provides in the specification other modes of administration. Further, one skilled in the art wold be familiar with other modes of administration.

The Applicants, therefore, submit that since the disclosure of the specification explains the mechanism of polyamines on DHS, the relationship of DHS to eIF-5A, the relationship of DHS and eIF-5A to apoptosis, an exemplary amount of agent (polyamine) to achieve the desired and claimed result (in a working example), modes of administration, and toxic levels to avoid, one skilled in the art would be able to use the disclosure to practice the claimed invention without undue experimentation.

Nevertheless, the Examiner seems to believe that the specification is only enabled for the one working example set out in Example 6. One does not need to prove enablement or show working examples for all of the claimed genus if there is enablement for a species, and if one skilled in the art could practice the invention without undue experimentation. In MPEP 2164.06, it states that in testing the amount of experimentation, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 731 (Fed. Cir. 1988). Applicants respectfully submit that the specification provides "a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" i.e. levels of spermidine administrated to successfully inhibit apoptosis and toxic levels to avoid, etc.

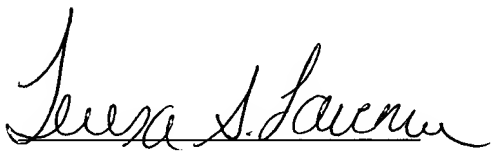
According to MPEP 2164.04, the burden is on the Examiner to specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. The Examiner has not done this and has stated that it was known that polyamines can cause different effects on cells. In doing so, as stated above, the Examiner has failed to consider the teachings and guidance of the specification that provide real working detailed examples on how to administer polyamines, as well as how much to administer to achieve the desired result (to inhibit apoptosis). Thus, the Examiner has not met his burden and accordingly, Applicants respectfully request withdrawal of this ground of rejection.

## CONCLUSION

Applicants submit that the claims are in condition for allowance. Although it is believed that no fees are necessary for the filing of this paper, Applicants authorize the Commissioner to charge the requisite fee for such extension as well as any other fee due or credit any overpayment arising from this communication to Deposit Account No. 11-0600.

Respectfully submitted,

Date: 11/12/03



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